THE COUNCIL FOR TOBACCO RESEARCH–U.S.A., INC.

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NEW YORK, N. Y. 10022
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Application for Research Grant
(Use extra pages as needed)

Date: July 20, 1973

1. Principal Investigator (give title and degrees):

Charles Mittman, M.D., Director, Department of Respiratory Diseases
Jack Lieberman, M.D., Associate Director, " " "

2. Institution & address:

City of Hope Medical Center
1500 East DuarteRoad
Duarte, California 91010

3. Department(s) where research will be done or collaboration provided:

Department of Respiratory Diseases, City of Hope Medical Center;
Medical Department, Kaiser Steel Corporation, Fontana, CA

4. Short title of study:

Hereditary Susceptibility to Bronchitis-Emphysema

5. Proposed starting date: October 1, 1973

6. Estimated time to complete: Two years

7. Brief description of specific research aims:

See attached pages for items 7 through 13

7. Brief description of specific research aims

Investigators have long suspected that inheritance can influence an individual's susceptibility to the damaging effects of his environment. Examples of genetic-environmental interplay leading to disease are accumulating in various fields of medicine. Such diseases are particularly important since they can be prevented if the genetic predisposition can be recognized prior to injury and the pathological process can be aborted by correction of the underlying defect or modification of the environmental factors. Data are accumulating which suggest that alpha$_1$-antitrypsin deficiency leads to chronic obstructive lung disease (COLD) through such a mechanism. This project seeks to develop the information needed to devise preventive programs for these diseases by:

1) Continuing the studies successfully initiated at the Kaiser Steel Mill, Fontana, California. Preliminary results suggest that information about a worker's inheritance can be used to make job placement recommendations which will benefit his future health.
2) Investigate the possibility of extending this study to steel mills in other locations so as to assess the role of climate, air pollution and other factors in the effects being observed.
3) Further evaluate a simplified, practical approach to detecting antitrypsin abnormalities in large populations.
4) Search for other identifiable genetic factors which could predispose to the development of lung disease. We will establish techniques to examine the level of proteases in leukocytes and determine if variations in this factor account for differences in susceptibility to lung disease. Further, patients with lung disease apparently related to familial factors will be examined in an attempt to identify causative genetic factors other than antitrypsin deficiency.

8. Working hypothesis

Interactions of genetic and environmental factors are involved in the etiology of a significant fraction of cases of chronic obstructive lung disease. Alpha$_1$-antitrypsin deficiency is one factor which predisposes to COLD by this mechanism. By studying industrial workers and selected patients we can 1) evaluate the importance of antitrypsin deficiency as a predisposing factor, 2) search for other identifiable inherited factors, 3) develop efficient means for screening large populations to identify individuals with genetic variants of alpha$_1$-antitrypsin, and 4) assess the role of various industrial, atmospheric and personal air pollutants in the genesis of clinical lung disease in genetically predisposed individuals. Such information can lead to the establishment of effective obstructive lung disease prevention programs.

9. Experimental design

Surveys will be continued at a plant of the Kaiser Steel Corporation located near the City of Hope Medical Center. This site has been selected because:

a) the industrial health department, management and labor are interested in this project and are cooperating fully with it.
b) the 5000 man work force is relatively stable.
c) the plant is an integrated metal mill and its various operations involve a wide range of dust, fume and smoke exposure levels. Large numbers of workers have had prolonged employment in various areas with well defined irritant levels (as coke oven workers, welders, grinders, aluminum workers).
d) workers who have been forced to retire or change jobs because of respiratory and other symptoms can be traced. Their detailed work records are available, and for those receiving medical care through the local Kaiser Health Plan, accurate medical histories can be obtained.
e) it is possible to bring selected subjects to the City of Hope Medical Center for further studies.

Blood samples are obtained and data collected by questionnaire at the plant. Standardized methods are used to obtain information on 1) work history and occupational and avocational lung irritant exposure now and in the past; 2) air pollution exposure at home and while commuting; 3) personal cardiopulmonary symptoms and smoking history, and 4) family history of cardiopulmonary disease, smoking habits of relatives with disease and ethnic background data.

Blood samples are analyzed for antitrypsin abnormalities (see below) and selected subjects are brought to the Medical Center for extensive studies of lung function in order to determine the following:

1) what abnormalities are seen in subjects with protease inhibitor variants as compared to those with the normal Pi phenotype. To isolate the independent influence of the protein abnormality, subjects are matched by age, sex, ethnic background, smoking history, occupation and other pertinent characteristics. Appropriate statistical methods are employed for data analysis.
2) do smoking, industrial air pollution exposure, place of residence and other factors particularly influence the lung function of subjects with various Pi types.
3) are individuals with a family history of lung disease particularly susceptible to lung disease without regard to Pi type.
4) which tests are most sensitive to early changes in lung function or structure and what significance do these changes have.

The test battery carried out at the Medical Center includes the following procedures:

1) spirometry with measurement of vital capacity, flow rates and flow-volume curves.
2) inert gas dilution and washout for measurement of lung volume, closing volume and ventilation efficiency.

3) diffusing capacity measured by the breathholding and steady state methods.
4) body plethysmography for measurement of lung volume and airway resistance.
5) rest and exercise ventilation. Arterial or capillary blood gas analysis for calculation of arterial-alveolar gradient can be performed on selected subjects.
6) standard chest radiographs.
7) scintillation camera lung scan for assessment of regional perfusion.
8) electrocardiograms.

Individuals with antitrypsin deficiency are considered to be ideal subjects for a study of the sensitivity of new tests of abnormalities of lung function and structure. The availability of detailed standard pulmonary function test results on deficient and matched control subjects and the opportunity to initiate a prospective study of such subjects will permit evaluation of the significance of abnormalities detected. For example, in addition to measuring diffusing capacity by the standard carbon monoxide steady state and breathholding methods, we use the so-called uptake-washout technique on all subjects. This test employs digital computer methods to examine ventilation and CO gas transfer in terms of a multicompartment model of the lung. Preliminary results of studies on volunteers with antitrypsin deficiency suggest that this method can reveal evidence of non-uniformity of lung function prior to the presence of abnormalities of overall function.

By sampling the entire work force of this plant, approximately 300 individuals with abnormal antitrypsin variants would be available for detailed study. Of this potential panel of 600 subjects (deficient and control) nearly one-fourth will have been seen at the Medical Center this year. The remaining subjects could be studied, if this is considered worthwhile, over the next 2 to 3 years. During the first year of this project we concentrated our studies on subjects who were deemed likely to yield the most clearcut findings. Studies of the coke oven area, indeed, suggest that our working hypothesis is correct and that information about a worker's inheritance can be used to make job placement recommendations which will benefit his future health. Continuation and expansion of this project is deemed essential to establish if the trends seen in these preliminary data are real.

Extension of These Studies to Other Geographical Areas:

Encouraged by our preliminary results we have initiated discussions to extend these studies to steel mills located in other areas of the country. If the techniques being used can effectively assess the health impact of various hazards and lung irritants, then sampling at different sites might permit us to determine the contribution of climate, residential air pollution and other variables. Preliminary contacts have evoked a favorable response and it is hoped that cooperative protocols can be developed over the coming year.

Characterization of Pi Phenotype:

Broad application of the findings of this study depends on a practical method for detecting Pi abnormalities in large populations. Pi phenotyping currently requires the use of the slow, tedious and expensive methods of acid starch gel and crossed antigen-antibody electrophoresis. Phenotyping cannot be performed as a primary approach to large numbers of sera. Methods for quantitating the amount or activity of protease inhibitor in serum are simple, inexpensive, reliable and reproducible. They lend themselves to automation and can be applied to large population studies. However, the overlap between the normal range and that seen in phenotypes associated with the intermediate deficiency limits the usefulness of these methods. A two-stage screening procedure appears to be a reasonable compromise between the need for definitive results and the limitations of time and expense.

Two approaches to a screening method have been examined by us. One involves defining limits for the concentration or activity assays which would establish with a high degree of assurance that a blood sample comes from a normal phenotype. For example, serum trypsin inhibitory capacity (STIC) assays can be done easily on large numbers of blood samples. It has been determined that all bloods with an STIC of 0.80 units or less are from individuals with deficient phenotypes. We have also established that 98% or more of blood samples with STIC values over 1.2 units have the normal or MM phenotype, so that such bloods need not be studied in any greater detail than an STIC assay. However, abnormal phenotypes are seen among the samples between these two ranges and such bloods account for nearly half of all samples from healthy subjects. Thus, screening by STIC does not eliminate the need for phenotyping large numbers of sera.

Another approach to a two-stage screening method is more promising. Serum antitrypsin levels can be easily quantitated by the immunodiffusion method. We have established that Pi phenotypes which most commonly yield deficient levels, the ZZ, MZ, SZ, SS and MS variants, give a characteristic double ring pattern on immunodiffusion assay when a special antibody is used. A commercially available method for performing this test will be evaluated in our laboratory during the coming year using bloods from this industrial survey as well as other samples.

Search for Other Genetic Factors:

It is clear that antitrypsin deficiency accounts for only a fraction of cases of lung disease associated with familial factors. Our laboratory has been interested in identifying, if possible, other factors. Defects of the immunoglobulin system do not account for any appreciable fraction of cases, nor do cystic fibrosis heterozygotes occur with any unexpected frequency among patients with chronic lung disease. Galdston, Janoff and Davis have recently suggested that an inherited variation in the level of a leukocytic lysosomal

protease influences the expression of alpha$_1$-antitrypsin deficiency (Amer Rev Resp Dis 107:718-727, 1973). To evaluate this hypothesis we will establish this method in our laboratory and test our patients and volunteer subjects for such activity. Further, patients with lung disease not associated with antitrypsin deficiency will be tested to determine if excessive quantities of protease could cause disease in individuals with normal inhibitor activity.

Finally, we will continue to survey patients for indications of familial tendencies toward lung disease and attempt to characterize the abnormalities in such patients. Individuals who have developed significant disease at an early age and without the prior exposures usually seen in such patients can offer important clues to underlying predisposing factors. The same can be said for patients who report a strong family history of lung disease. We have been studying intensively such patients seen on our clinical service. During the coming year the principal investigator will have an unusual opportunity while on sabbatical leave in Israel to extend these exploratory studies. Data collected by our laboratory and preliminary data from Israel suggest that antitrypsin deficiency is rare among Jewish and Arab patients with chronic obstructive lung disease. This question will be systematically examined by performing antitrypsin assays and collecting standardized clinical data on approximately 400 patients in the Tel Aviv area. Unusual prevalence rates for lung disease will be sought in various highly inbred population groups residing in that area. We are aware, for example, that early onset of severe bronchitis is common in men in the colony of Samaritan Jews residing in Israel. We have participated in a preliminary cooperative study which suggests that antitrypsin deficiency plays no role here. This will be further examined and the type and degree of lung disease present in such groups will be assessed in the field by spirometry and, as indicated, by more complete tests in a hospital pulmonary function laboratory.

10. Physical Facilities Available

Laboratory Facilities: The research and support facilities available at the City of Hope Medical Center are more than adequate to carry out the project outlined here.

Lung Biochemistry Laboratory: A fully equipped 1600-square foot laboratory is available to this project. Equipment includes a Gilford Model 2400 spectrophotometer, Radiometer pH stat, Gilford Model 300 microspectrophotometer, Beckman microzone electrophoresis equipment, a Gelscan apparatus, Gelman immunoelectrophoresis and Bucher Starch Gel Electrophoresis equipment, an IL flame photometer, Kahn surface tension balance and refrigerated centrifuge. Facilities include a walk-in cold room, small animal room, animal exposure chamber and hood.

Human Physiology Laboratory: The clinical pulmonary physiology laboratory occupies 1200-square feet. Its equipment includes Collins and Wedge spirometers, treadmill, a pressure body plethysmograph, Radiometer micro blood gas analyzer, electronic analyzers for CO2, CO, He and N_2, an 8-channel Sanborn recorder, a 7-channel Sanborn analog tape recorder and a laboratory computer (PDP 12) with 8K memory, two digital tape units, hardware arithmetic, 16-channel A to D and D to A converters, CRT and teletype communication device. The laboratory now operates 8 hours per day including week ends in order to accommodate the added work load of this project and to facilitate the study of subjects who are employed full time.

Animal Physiology Laboratory: Although not directly involved in the present project, approximately 200 square feet in the animal laboratory is assigned to the Respiratory Disease Department. Equipment includes a Radiometer blood gas analyzer, an 8-channel E for M recorder, Harvard respirator and electronic analyzers for CO and He gas. The animal laboratory also has radiology equipment available for fluoroscopy and general radiography.

Other Clinical Laboratory Units: Each clinical department has laboratory facilities which, as needed, are available to this project.

Basic Science Laboratories: The City of Hope Medical Center complex includes Basic Science Divisions which house and support the research programs of over 50 PhD investigators. Major research areas include genetics, molecular biology, neurosciences, experimental pathology and immunology. Although not directly involved in this program, these units are available for consultation, collaboration and equipment support. The small relative size of the Medical Center staff and the geographic proximity of all departments contribute to the ease of communication between the medical and scientific staff. Consultation is available on problems of molecular genetics from such investigators as Dr. Susumu Ohno of the Biology Division.

Biomathematics: The Biomathematics Department offers computer and statistical support and consultation service and serves as a tie to the UCLA Health Sciences Computer Facility and its staff. An IBM 2780 teleprocessing terminal gives access, over phone lines, to the IBM 360/91 computer at the UCLA Health Sciences Computer Center. Computer service is on a daily, batch job basis with turnaround within 12 hours. The terminal consists of a high speed card reader and punch and a 300-line per minute printer. All programs of the UCLA Biomed series are available as are excellent machine file storage service and Fortran and PL 1 programming support.

Clinical Facilities: The City of Hope Medical Center includes a 200-bed hospital and an outpatient department located on a 90-acre site 25 miles east of Los Angeles. The annual budget of the institution exceeds $16 million, with partial support of basic and clinical investigation programs derived from research grants totalling over $2 million annually. Clinical programs concentrate on the care of adult and pediatric patients with serious medical and surgical diseases of the lungs, heart, blood and the metabolic and endocrine apparatus. The Medical Center also has clinical services for cancer surgery, neurology and neurosurgery (especially pain problems) and medical genetics. Patients are accepted for diagnostic evaluation and therapy on referral from private physicians. Medical care is given at no cost to the patient; these costs are supported by a private, national fund raising organization. The medical staff numbers over 60 full time specialists; most hold faculty appointments at local medical schools. All necessary support services, including clinical and anatomic pathology and diagnostic and therapeutic radiology, are represented by the full time staff. A consulting staff of specialists from the local medical community augments the full time staff as consultants in fields not represented on the staff.

The Respiratory Disease Department is one of five units in the Division of Medicine. It is presently staffed by five internists who direct the care on a 36-bed inpatient service and attend in an outpatient clinic one morning per week. Patients represent the entire spectrum of chest diseases, which includes acute and chronic obstructive lung disease, lung cancer, pulmonary fibrosis, tuberculosis, other acute and chronic infectious diseases and various diagnostic problems. Programs of special interest, such as one to manage young adults with cystic fibrosis, have been established in conjunction with clinical research projects. Inpatient care is facilitated by the geographical grouping of all patients, staff offices and support services. The staff of the inpatient service includes a full time social worker, a pharmacist (who acts as a consultant and administers a unit dose drug system) occupational and physical therapists and a clinical nurse specialist. This nurse is trained in physical medicine in addition to nursing and serves as a resource person for the nursing staff and patients (in- and outpatients). The nursing staff is large and stable. An inhalation therapy service, administered by the Respiratory Disease Department, supplies the therapy needs of the chest patients and the rest of the hospital.

The other services within the Division of Medicine are the Departments of Cardiology, Hematology, Medical Genetics and Metabolic Diseases. Although not directly involved in this program, their fourteen staff members supply necessary consultative and collaborative support and supervise specialized facilities such as the Cardiac Catheterization Laboratory, Electrocardiography and Vectorcardiography Laboratory, and Genetics Counselling Service. These medical departments also have active outpatient services, manage approximately 60 inpatient beds, and have their own programs of clinical investigation. Research programs in medical genetics are of special significance to the project outlined here. Active consultation is available on an ongoing basis from Drs. Ernest Beutler of the Hematology Department and David Comings of the Medical Genetics Department on problems of population genetics and molecular biology.

The Division of Radiology includes a Therapy and a Diagnostic Department and has a staff of eight physicians. Diagnostic equipment available includes two fluoroscopic machines with closed circuit television monitors and image intensifiers. These are equipped with 16 and 35mm cine and kinescope, as well as videotape recording capability. Two conventional linear systems for body section radiography and one system for transverse layerographs are available. Three rooms are equipped for chest, general radiography, and xeroradiography. The surgical suite is equipped with three x-ray installations; one is a complete catheterization lab facility and has 35mm cine along with TV monitoring of the image intensifier. Rapid film changing devices include a bi-plane Elema, a single plane Sanchez-Perez and a single plane Elema changer. The therapy service handles approximately 50 patients at any one time and its equipment includes a Theratron Cobalt 60 unit. In addition, equipment in the radioisotope diagnostic laboratory includes a scintillation camera, 5-inch crystal Picker Magna Scanner and Picker Dual Probe Ratemeter.

Other clinical divisions include Anesthesiology, Surgery and Neurology. The Anesthesiology Service is composed of four physicians, Cardiovascular Surgery includes a Thoracic Surgery Service with two senior staff members and Oncological Surgery with three. Surgical residents, rotated from local medical schools, augment the staff of the latter services. The Neurology and Neurosurgery staff serve as consultants on problems of pain and in other specialized areas. These services direct approximately 60 inpatient beds and also have active outpatient services. The Pediatrics Department includes a 20-bed inpatient service and an outpatient clinic devoted largely to the care of children with hematologic and solid tumors. Pediatric pulmonary problems of special interest are periodically accepted and cared for jointly with the Respiratory Disease Department. Cardiac, solid tumor, and other types of pediatric patients are handled in a similar joint fashion. The Pathology Division with seven staff members includes Departments of Clinical and Anatomic Pathology and of Cytology and Cytogenetics. Facilities include automated chemistry equipment and light and electron microscopes.

In addition to these inpatient and outpatient facilities, the Medical Center has housing on its grounds for ambulatory care patients. Office, space, business equipment and furniture and other support facilities necessary for the conduct of the projects described here are readily available.

Other Support Facilities: Other support services, such as a Medical Library and an Electronics Instrumentation Repair and Development Laboratory, are available on the Medical Center grounds.

Facilities for Studies to be Performed at the Tel Aviv University: During his sabbatical leave the principal investigator will be affiliated with the Chaim Sheba Medical Center, a large government hospital which serves as a teaching unit of the School of Medicine, Tel Aviv University. Facilities there include an active inpatient and outpatient chest service and a pulmonary function laboratory equipped to perform routine studies as well as to measure diffusing capacity, lung compliance, work of breathing and arterial blood gases. The institution has agreed to make these facilities available part-time for studies as outlined in this proposal. Space is also available to carry out the antitrypsin assays outlined.

11. BIOGRAPHICAL SKETCH: CHARLES MITTMAN

Title: Director, Respiratory Disease Department

Birthdate: R

Place of Birth: Chicago, Illinois

Education: A.B. University of Chicago, R
B.S. " "
M.D. " "

Honors: Alpha Omega Alpha; Sigma Xi; A.B., B.S., M.D. with honors

Major Research Interest: Pulmonary Physiology

Research and/or Professional Experience:

Director, Respiratory Disease Department, City of Hope Medical Center, Duarte, California, 1966-present
Associate Clinical Professor of Medicine, University of California at Los Angeles, 1973-present
Assistant Clinical Professor of Medicine, University of California at Los Angeles, 1967-73
Instructor, Department of Medicine, University of Chicago, 1/66-12/66
USPHS Post-doctoral Fellow, Department of Medicine, University of Chicago, 7/65-6/66.
Assistant Resident in Medicine, University of Chicago Clinics, 7/64-6/65
Assistant in Medicine, Johns Hopkins University School of Medicine, Baltimore, 7/63-6/64
Assistant Visiting Physician in Medicine, Baltimore City Hospital, 2/62-6/64
Surgeon, USPHS, Gerontology Branch, National Heart Institute, Baltimore City Hospital, 12/61-6/64

McCoy College of Johns Hopkins University, elective courses in Mathematics 9/62-64.
University of Chicago, Committee on Mathematical Biology, 7/65-6/66

PUBLICATIONS - CHARLES MITTMAN

1. Mittman C: Nonuniform pulmonary diffusing capacity measured by sequential CO uptake and washout. J Appl Physiol 23:131-138, 1967.

2. Mittman C, Lieberman J, Marasso F and Miranda A: Smoking and chronic obstructive lung disease in alpha$_1$-antitrypsin deficiency. Chest 60:214-221, 1971.

3. Mittman C, editor. Pulmonary Emphysema and Proteolysis. Academic Press NY, 1972.

4. Mittman C, Barbella TV and Lieberman J: Alpha$_1$-antitrypsin deficiency as an indicator of susceptibility to pulmonary disease. J Occup Med 15:33-38, 1973.

5. Mittman C, Barbella TV and Lieberman J: Alpha$_1$-antitrypsin deficiency and abnormal protease inhibitor phenotypes in patients with lung disease. Arch Environ Health. In press.

11. BIOGRAPHICAL SKETCH: JACK LIEBERMAN

Title: Associate Director, Department of Respiratory Diseases

Birthdate: R

Place of Birth: Chicago, Illinois

Education: B.A., University of California at Los Angeles, R
M.D., University of Southern California, R

Major Research Interest: Pulmonary Biochemistry

Research and/or Professional Experience:

Associate Director, Respiratory Disease Department, City of Hope Medical Center, Duarte, California, 1968-present.
Associate Clinical Professor of Medicine, University of California at Irvine, 1971-present.
Associate Clinical Professor of Medicine, University of California at Los Angeles, 1968-71.
Section Chief, Internal Medicine, Veterans Administration Hospital, Long Beach, California, 1963-68.
Clinical Investigator, Veterans Administration Hospital, Long Beach, 1960-63.
Research Fellowship (Heart), Harbor General Hospital, Torrance, California, 1958-60.
Attending Staff, Harbor General Hospital, Torrance, 1960-present
Consultant, Memorial Hospital of Long Beach, 1968-present
Consultant, Veterans Administration Hospital, Long Beach, 1968-present.

PUBLICATIONS - JACK LIEBERMAN

1. Lieberman J: Digestion of antitrypsin-deficient lung by leukoproteases. Pulmonary Emphysema and Proteolysis, pp 189-203. C. Mittman, editor. Academic Press, NY and London, 1972.

2. Lieberman J and Kaneshiro W: Inhibition of leukocytic elastase from purulent sputum by alpha$_1$-antitrypsin. J Lab & Clin Med 80:88-101, 1972.

3. Lieberman J, Mittman C and Gordon HW: Alpha$_1$-antitrypsin in the livers of patients with emphysema. Science 175:63-65, 1972.

4. Lieberman J and Mittman C: A new "double-ring" screening test for carriers of alpha$_1$-antitrypsin variants. Amer Rev Resp Dis, in press.

5. Lieberman J: Heat lability of alpha$_1$-antitrypsin variants. Chest, in press.

BIOGRAPHICAL SKETCH: E. EUGENE PEDERSEN

Title: Consultant in Epidemiology

Birthdate: R

Place of Birth: Milwaukee, Wisconsin

Education: B.A. California State College, Long Beach, R
M.A. California State College, Long Beach,
PhD. Claremont Graduate School and
University Center, R

Honors: Psi Chi, National Honorary Society in Psychology, 1960
Dean's List, California State College, Long Beach
(5 semesters) 1960-62

Major Research Interest: Biostatistics, research design, population study & enviornmental stress effects

Research and/or Professional Experience:

Co-Investigator, USC/Rancno Los Amigos Hospital, Downey, CA. Statistician and Epidemiologist 1970-present.
Co-Investigator, USC/Rancho Los Amigos Hospital, Downey, CA. Programs developed to study Behavioral Effects of Environmental Stressor Agents 1970-present.
Assistant Professor of Psychology, California State University at Los Angeles 1970-present.
Lecturer, USC School of Education 1969-70.
Instructor, Pepperdine University, Research Design and Statistics, 1967.
Research Psychologist, Vocational Services, Rancno Los Amigos Hospital, Downey, CA 1967-70.
Research Associate, Rancho Los Amigos Hospital, Downey, CA, Attending Staff Association 1965-66.
Graduate Assistant, California State College at Long Beach, Experimental Psychology and Learning Labs 1964-65.
Research Assistant, Psychology Department, V A Hospital, Long Beach, CA 1961-64.

PUBLICATIONS - E. EUGENE PEDERSEN

1. Wendlend LV, Forney RL, Pedersen EE and Coss JG: The use of automated instruction with severely physically handicapped students. J Natl Soc for Programmed Instruct 6:(10) 409, 1967.

2. Coss JG, Forney RL, Wendland LV, Pedersen EE: Effectiveness of automated visual programmed instruction with paraplegic and other severely handicapped students, Final Report. Project No. 5-0411., U. S. Office of Education, Dept. of Health, Education and Welfare, December 1966.

3. Wetmore C and Pedersen EE: Selection of students for orthotic-prosthetic education programs. Prosthetic Res.Bull, Fall, 1969,ed.

4. Pedersen EE, Breisacher P and Hackney JD: Rapid assessment of tests of pollutant effects in man. Institute of Environmental Sciences, 1971 Proceedings "Living in Our Environment," 277-281, 17th Annual Technical Meeting, Biltmore Hotel, April 26-31, 1971.

14. First year budget:

A. Salaries (give names or state "to be recruited") Professional (give % time of investigator(s) even if no salary requested)	% time	Amount
*C. Mittman, MD, Principal Investigator	30%	
J. Lieberman, MD, Co-Investigator	20%	
**E. Pedersen, PhD, Consultant in Epidemiology	5%	
Technical		
T. B. Barbela, Research Technician	20hr	
L. Gaidulis, Biochemistry Technician	20hr	
W. McClelland, Pulmonary Function Tech	20hr	
***To be filled, research Tech in Israel	40hr	
Sub-Total for A		
B. Consumable supplies (by major categories)		
Blood drawing and storage	1,000	
Reagents, antibodies	1,000	
Gases, recording paper, forms, etc.	1,000	
Sub-Total for B		3,000
C. Other expenses (itemize)		
Computer time	500	
Repair of equipment, maintenance	500	
Local travel for survey work	500	
Travel to scientific meetings	1,000	
****Fee paid to subjects brought to Medical Center in lieu of their day's wages	4,500	
Sub-Total for C		7,000
Running Total of A + B + C		28,137
D. Permanent equipment (itemize)		
*****Field spirometer for survey work	800	
Sub-Total for D		800
E. Indirect costs (15% of A+B+C)		4,671
Total request		36,608

*,**,***,****,*****, see notes on next page

15. Estimated future requirements

	Salaries	Consumable Suppl.	Other Expenses	Permanent Equip.	Indirect Costs	Total
Year 2	R	300	7,000	1,000	2,993	33,943
Year 3	None					

14A. Notes on budget items

* During the period of this grant Dr. Mittman will be on sabbatical leave at the Chaim Sheba Medical Center, Tel Hashomer, Israel, a unit of the School of Medicine, Tel Aviv University. He will directly pursue selected aspects of this project described in the proposal and will remain in contact with the activities at the City of Hope through correspondence and several week-long visits scheduled during the leave period. The day-to-day supervision of activities at the City of Hope will be the responsibility of Dr. Lieberman, the co-investigator.

** Dr. Eugene Pedersen, Epidemiologist, Respiratory Research Unit, Rancho Los Amigos Hospital, University of Southern California, has been serving as a consultant to this project and will continue in this capacity. He spends one to two days each month at the City of Hope and is receiving R per month, the customary fee at this institution. His biographical sketch is included.

*** These funds will be sufficient to hire a full time research technician in Israel to perform antitrypsin assays and carry out the pulmonary function studies outlined in the proposal.

**** During the current grant period Kaiser Steel employees who have come to the City of Hope for detailed studies have been transported at the expense of Kaiser and have received their usual wages for the day from the company. For the coming year the company has indicated that funds to cover these wages will not be available. We propose to compensate each man selected for studies at the Medical Center by paying them a fee of $30, an arrangement that is satisfactory to management and the union representatives.

***** The field spirometer will be used for studying various subjects in Israel, as outlined in the proposal.

16. Other sources of financial support:
List financial support from all sources, including own institution, for this and related research projects.

CURRENTLY ACTIVE

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates
Genetic and Environmental influences on lung disease	NIH 12833	30,301	9/1/73 to 8/31/74
Alpha$_1$-antitrypsin deficiency in pulmonary emphysema	NIH 13398	49,480	1/1/73 to 12/31/73

PENDING OR PLANNED

Title of Project	Source (give grant numbers)	Amount	Inclusive Dates
NONE			

It is understood that the investigator and institutional officers in applying for a grant have read and accept the Council's "Statement of Policy Containing Conditions and Terms Under Which Project Grants Are Made."

Principal investigator

Typed Name Charles Mittman

Signature [signature] Date 7/13/73

Telephone 213 (Area Code) 359-8111 (Number) 771 (Extension)

Checks payable to

City of Hope Medical Center

Mailing address for checks

1500 East Duarte Road

Duarte, California 91010

Responsible officer of institution:

Typed Name Elihu King

Title Assistant Administrator

Signature [signature] Date

Telephone 213 (Area Code) 359-8111 (Number) 709 (Extension)

10035397788